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June 10, 2002

Dockets Management Branch
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Docket No. 02P-0170
Response of Teva Pharmaceuticals USA
To Amarin Pharmaceuticals Citizen Petition

Teva Pharmaceuticals USA (Teva) submits these comments to the April 19, 2002 petition submitted by Amarin Pharmaceuticals (Amarin) which sets forth some conditions of bioequivalence, safety, degradation and stability which Amarin believes must be met before FDA may approve any abbreviated new drug applications, including Teva's, for pergolide mesylate tablets, the generic version of Permax®.

In its petition, Amarin requests that FDA ensure that ANDA's relying on the reference drug Permax not be approved in the absence of (1) data to demonstrate in vivo bioequivalence to Permax for all dosage strengths, (2) appropriate criteria for pergolide mesylate degradation products, and (3) acceptable stability data for all dosage strengths. Insofar as the requested information represents standard data requirements associated with approval of every ANDA product, Teva does not object to this petition. However, Teva does take issue with the manner in which Amarin characterizes some of the requirements for approval. Amarin's discussion points are addressed below.

1. The ANDA's Must Establish In Vivo Bioequivalence to Permax at All Dosage Strengths Based on an Appropriate Assay for Measuring Pergolide Absorption.

Amarin argues that there can be no assurance of equivalence for the different generic pergolide formulations absent the submission of in vivo bioequivalence data for all strengths. Given the known pharmacokinetics of pergolide mesylate (linear kinetics), if the formulations of the three strengths are proportionally similar and exhibit similar dissolution behavior, in vivo bioequivalence studies for all strengths are not required by FDA guidance. As mentioned below, bioequivalence studies were conducted on the low strength tablet. For this particular drug product, conducting an in vivo study on a strength that is not the highest strength is appropriate for safety reasons as exposing human subjects to higher doses creates a severe safety issue.

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Amarin appears to argue that ANDA applicants must establish bioequivalence based on the study of the 0.05 mg strength since "[s]pecial issues may be raised by the 0.05 mg dosage strength in light of its high excipient to drug ratio and the associated stability/degradation

concerns" as well as the role of the 0.05 mg strength in the titration of the drug. Amarin argues that an adequate method for measuring plasma levels of a low dose of the 0.05 mg pergolide mesylate tablets has not been developed to date and hence no generic applicants can have adequate bioequivalence studies. Amarin points out that Lilly's 1988 approvable letter required that Lilly work on the development of an appropriate assay as a condition of approval.

In fact there does exist methodology to adequately measure blood levels from low dose therapy. Teva has submitted an acceptable bioequivalence study with a validated analytical method on the 0.05 mg strength tablet formulation based on a protocol that was prospectively reviewed and approved by the Division of Bioequivalence. The fact that Lilly has apparently been unable to meet their commitment to FDA as a condition of their approval after the passage of fourteen years to develop an "appropriate assay" is a matter for FDA to address with Lilly.

Lastly, analogies to Premarin do not bear scrutiny. The rationale behind the lack of approvals for generic versions of Premarin have no bearing on the product at hand since the active moiety is identified, well-defined and measurable in the case of Permax.

2. Once an Assay is Available, Consideration Should be Given to the Need for Establishing Bioequivalence as to Pergolide Metabolites.

Amarin asserts (1) that evidence of activity of the pergolide sulfone and pergolide sulfoxide metabolites in animals bears relevance to the existence of any such activity in humans, and (2) that the metabolites should be measured because they are formed as the result of gut wall or other presystemic metabolism. Neither of these assertions is supported by data or reference thereto and amounts to pure speculation. In fact, the guidance to which Amarin refers, FDA's *Guidance for Industry, Bioavailability and Bioequivalence Studies of Orally Administered Drug Products —General Considerations*, succinctly states that:

> "For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite...."

Amarin has not established either that the metabolites are formed as a result of gut wall or other presystemic metabolism or that the metabolite contributes meaningfully to safety and/or effectiveness. In fact the Permax insert indicates that "Nothing can be concluded about the extent of presystemic clearance, if any." Without data demonstrating this there is simply no basis for requiring measurement of metabolites and FDA has obviously concurred by the acceptance of our protocol.

3. The Statements of the ANDA Applicants that the Proposed Generic Formulations do not Contain Equivalent Stabilizers to Permax Raise Serious Questions About the Stability and thus the Safety of the Generic Formulations.

Quite simply, if the generic applications for pergolide mesylate tablets did not contain a minimum of 12 week accelerated and 3 months room temperature stability data at the time of filing, the applications would not have been accepted. If the stability data submitted were not acceptable or did not meet the minimum specifications as established by FDA, the applications would simply not be approved. Teva has not only provided the minimal acceptable amount of stability data but has also included full real time (24 month) room temperature data for **all** strengths of our proposed tablet products (even the 0.05 mg) which meet all specifications as

reviewed by FDA. The mere existence of a patent does not preclude the invention of a different formulation which exhibits acceptable stability data but which falls outside the claims or scope of the patent on the reference listed drug.

4. The ANDA's Should Establish Acceptance Criteria for Pergolide Sulfoxide.

Without revealing confidential details of Teva's ANDA we can say that the specifications submitted in Teva's application have been reviewed by FDA. With their expertise and knowledge of the criteria established for Permax with regard to pergolide sulfoxide, FDA will ensure that Teva's specifications are appropriate.

5. The ANDA's Must Contain Stability Data to Support Expiration Dating.

All ANDA applicants are required to provide FDA with acceptable stability data to support the shelf life proposed within their application in order to gain approval. The FDA has the expertise to review such data and make determinations regarding acceptable expiration dating to ensure a stable product that meets all appropriate specifications over its proposed shelf life.

6. The ANDA's Should Establish Photostability.

Teva's product has been shown to be stable for a period of at least 24 months in the container/closure configuration intended for the commercial marketing of the product. The Teva product labeling provides the identical storage recommendations as the Permax labeling but in addition also contains the following instructions to the dispensing pharmacist which is standard wording in Teva labeling: "Dispense in a tight, light-resistant container as defined in USP, with a child-resistant closure...." This standard wording has been found acceptable by the FDA for inclusion on Teva labeling.

Conclusion

It is Teva's belief that the Amarin petition contains no substantive scientific or regulatory arguments and merely asks the FDA to impose the requirements that are already imposed on every ANDA applicant. It is clearly a transparent attempt to achieve additional market protection for Permax, a product for which Amarin recently acquired exclusive U. S. marketing rights, by delaying the approval of ANDA's. Teva respectfully requests that FDA, in their consideration of the contents of Amarin's petition, recognize this as well as the fact that no true issues of science have been raised by Amarin. In light of this, Teva requests that approval of its ANDA not be delayed any further by this petition.

Respectfully submitted,

Deborah Jeshot

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Part # 156148 NRIT 1-02